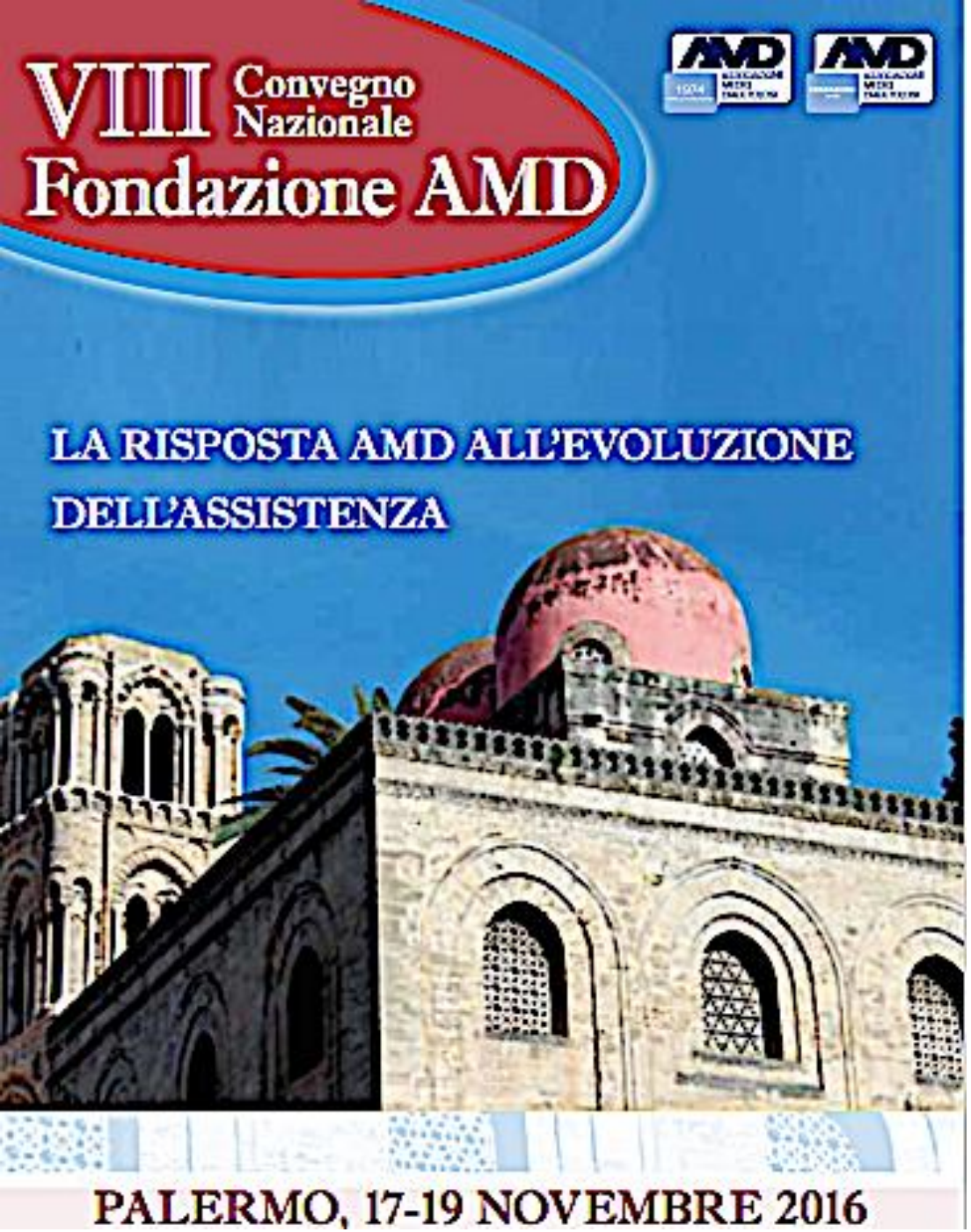


Quando serve l'insulina prandiale: l'importanza della PPG

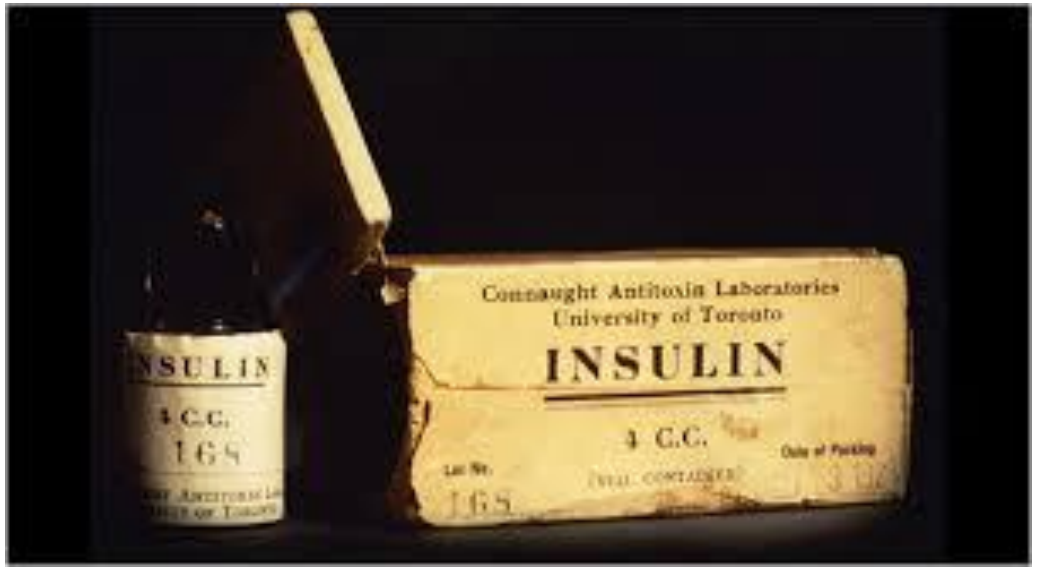
Giorgio Grassi

Endocrinologia Diabetologia e Metabolismo

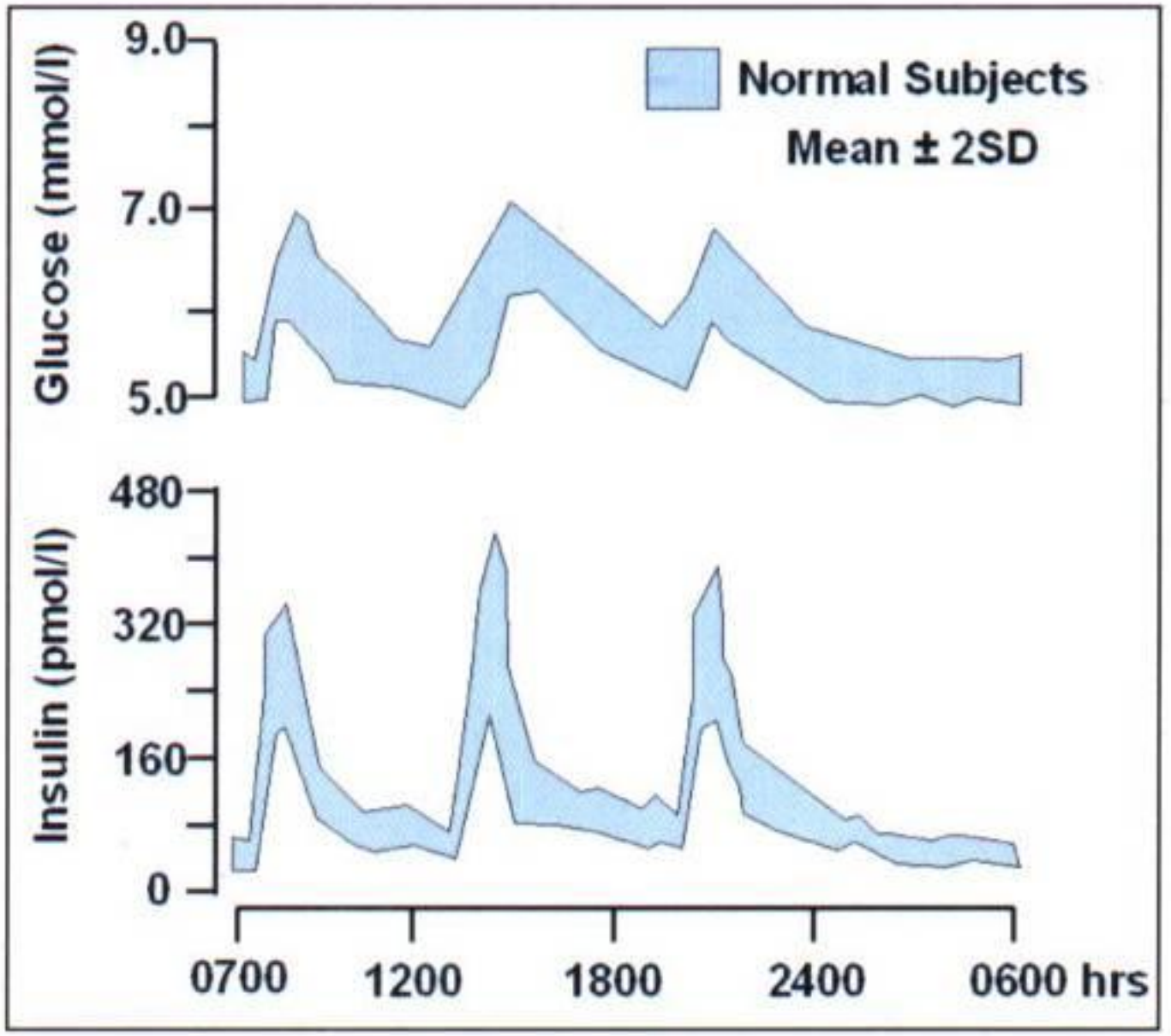
Città dellA Salute e della Scienza

Torino

Fisiopatologia e definizione della iperglicemia postprandiale



24-h plasma glucose and insulin profiles in healthy individuals



Bolli G, et al.lancet, 2001; 358: 739-746

Sequenza patogenetica nel diabete Tipo 2

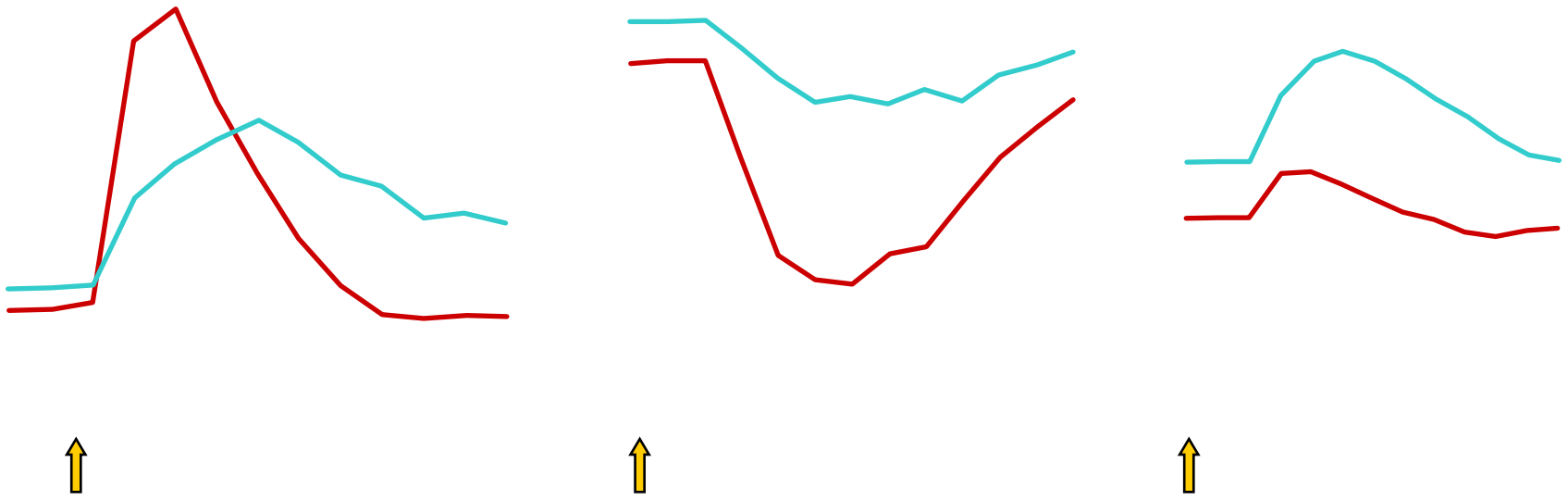
1
Ridotta secrezione
Precoce di insulina

2
Ridotta soppressione
della produzione
epatica di glucosio

3
Iperglicemia
post-prandiale

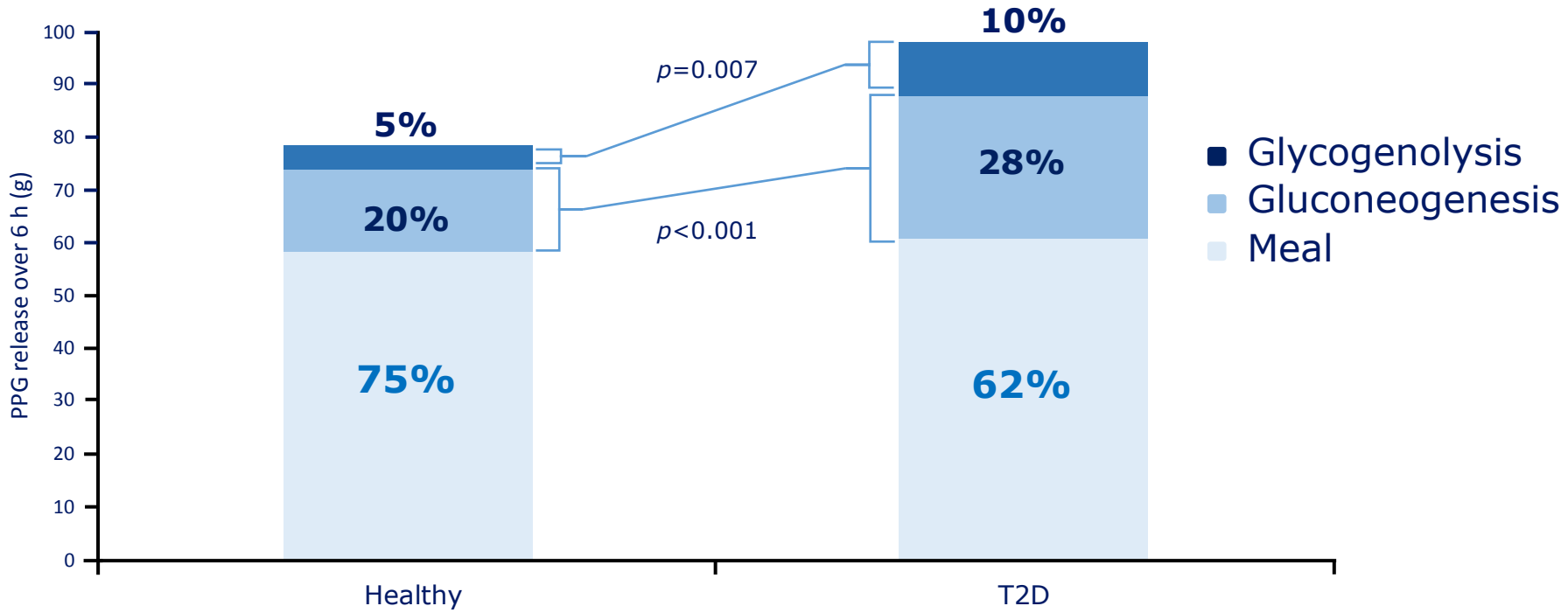
controlli

NIDDM



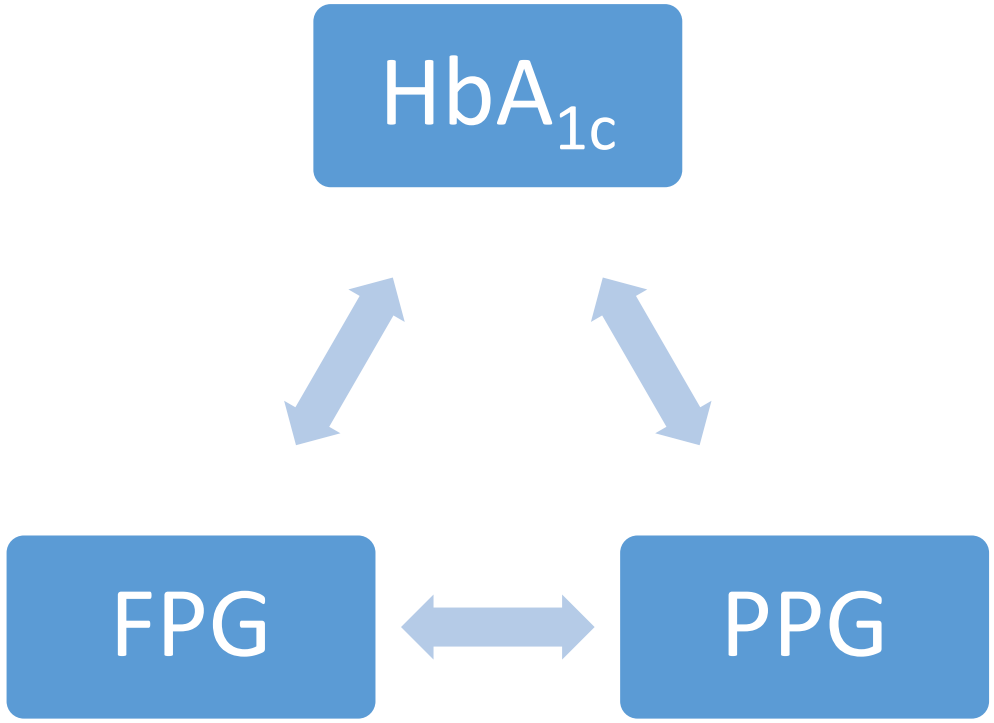
Ingestione di glucosio

Mechanisms for abnormal postprandial glucose metabolism in type 2 diabetes



Woerle et al. Am J Physiol Endocrinol Meatb 2006

Relationship between fasting and postprandial glucose with HbA_{1c}



Increased PPG and FPG drive increase in HbA_{1c}[1]

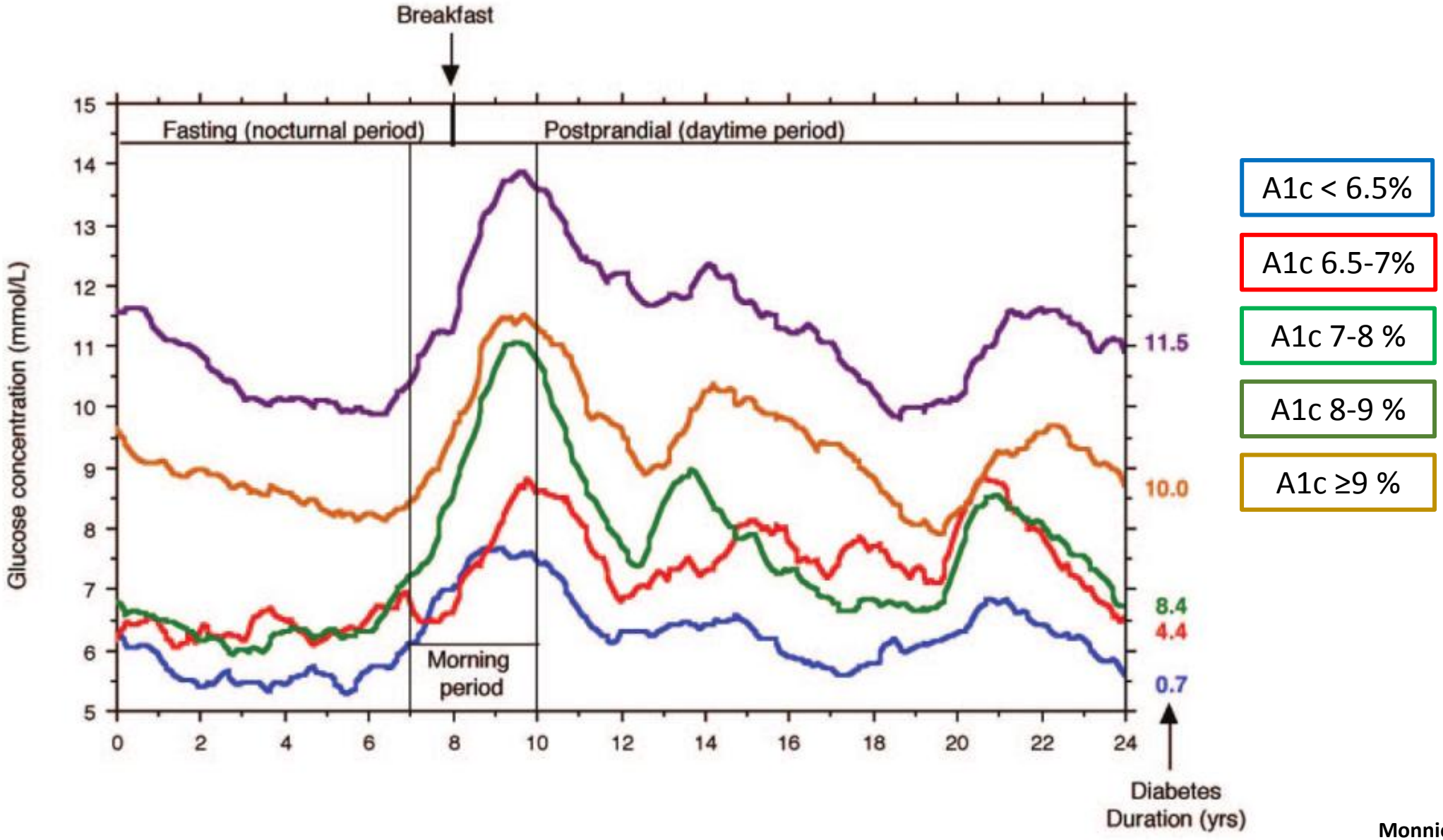
PPG is the predominant contributor in patients with satisfactory to good control of diabetes, whereas the contribution of FPG increases with worsening diabetes[2]

A recent meta-analysis found that

PPG has a stronger correlation with HbA_{1c} than FPG[3]

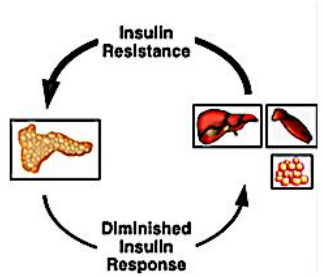
1. Monnier *et al. Diabetes Care* 2007;30:263–9; 2. Monnier *et al. Endocr Pract* 2006;12:S1:42–6; 3. Ketema *et al. Arch Public Health* 2015;73:43

The Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting With Worsening Diabetes

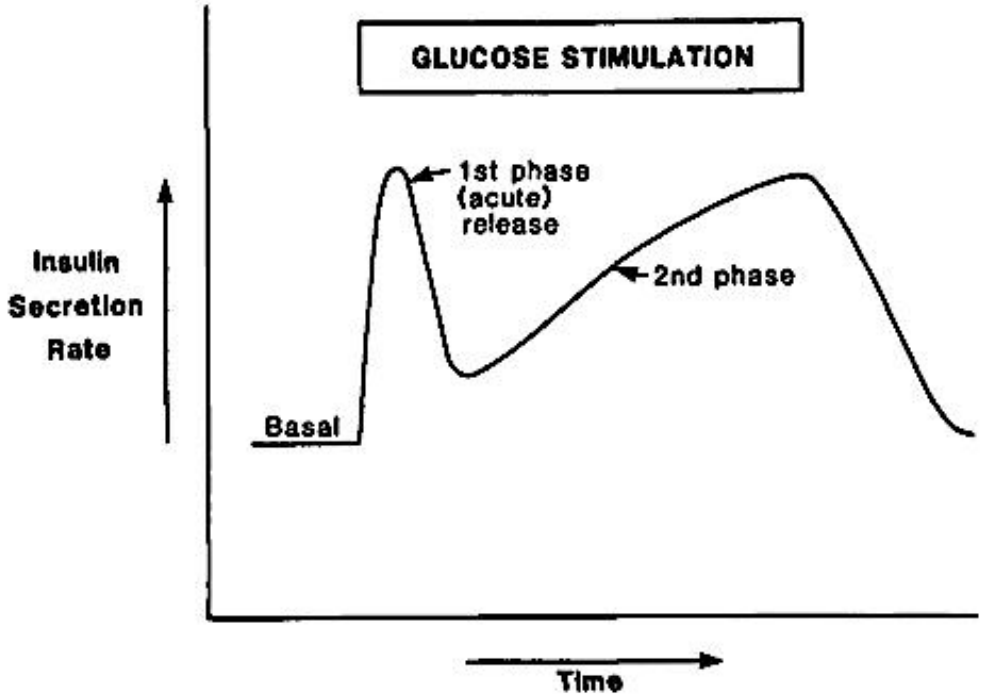


Monnier et al.Diabetes Care 2007

Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus



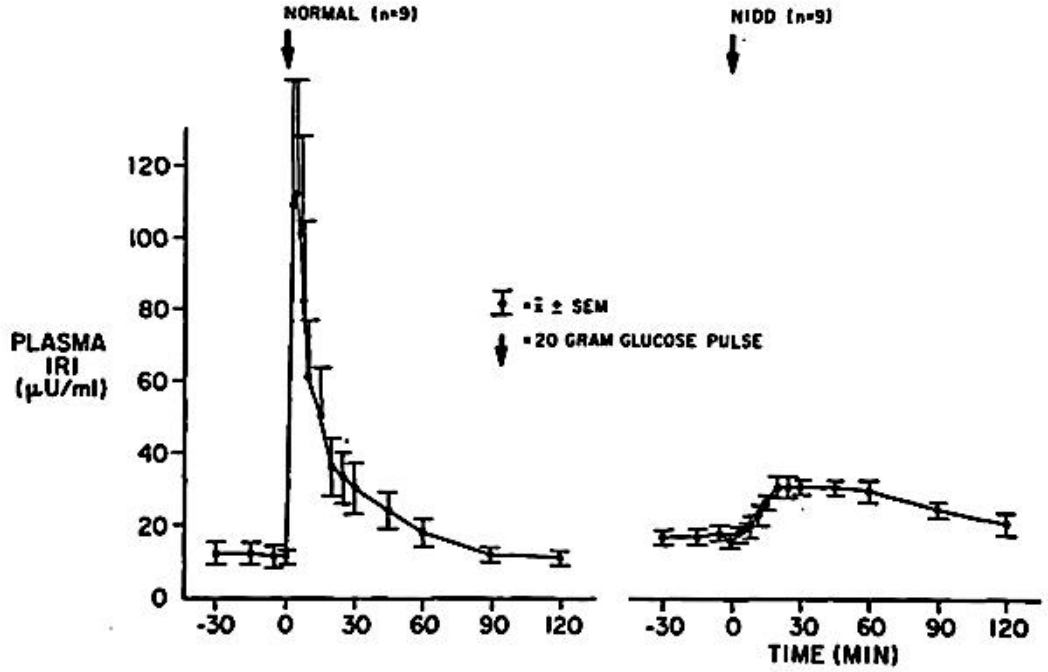
The biphasic insulin response. The peak of the first phase in man is between 3 and 5 min and lasts 10 min. The second phase begins at 2 min but is not evident until 10 min has passed.



Diabetes Care 1984,7, 491

Insulin *release in response to the intravenous administration of glucose in normal and diabetic subjec*

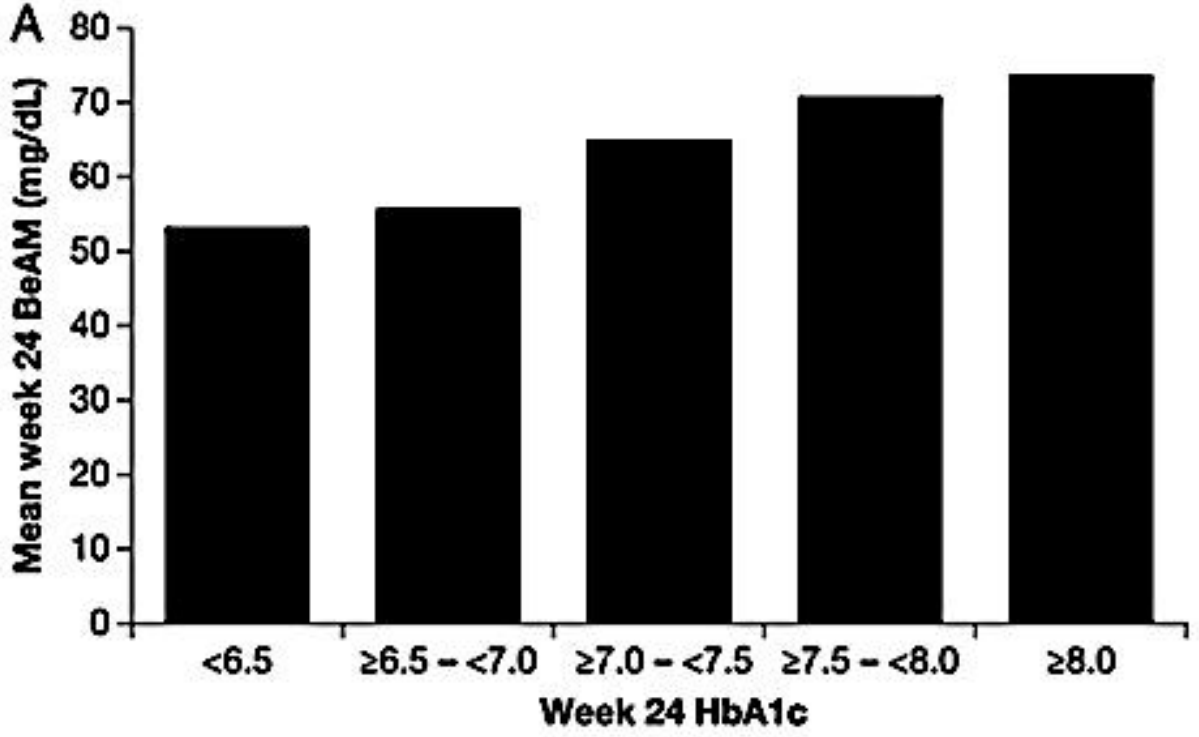
Lancet. 2014 March 22; 383



BeAM value: an indicator of the need to initiate and intensify prandial therapy in patients with type 2 diabetes mellitus receiving basal insulin

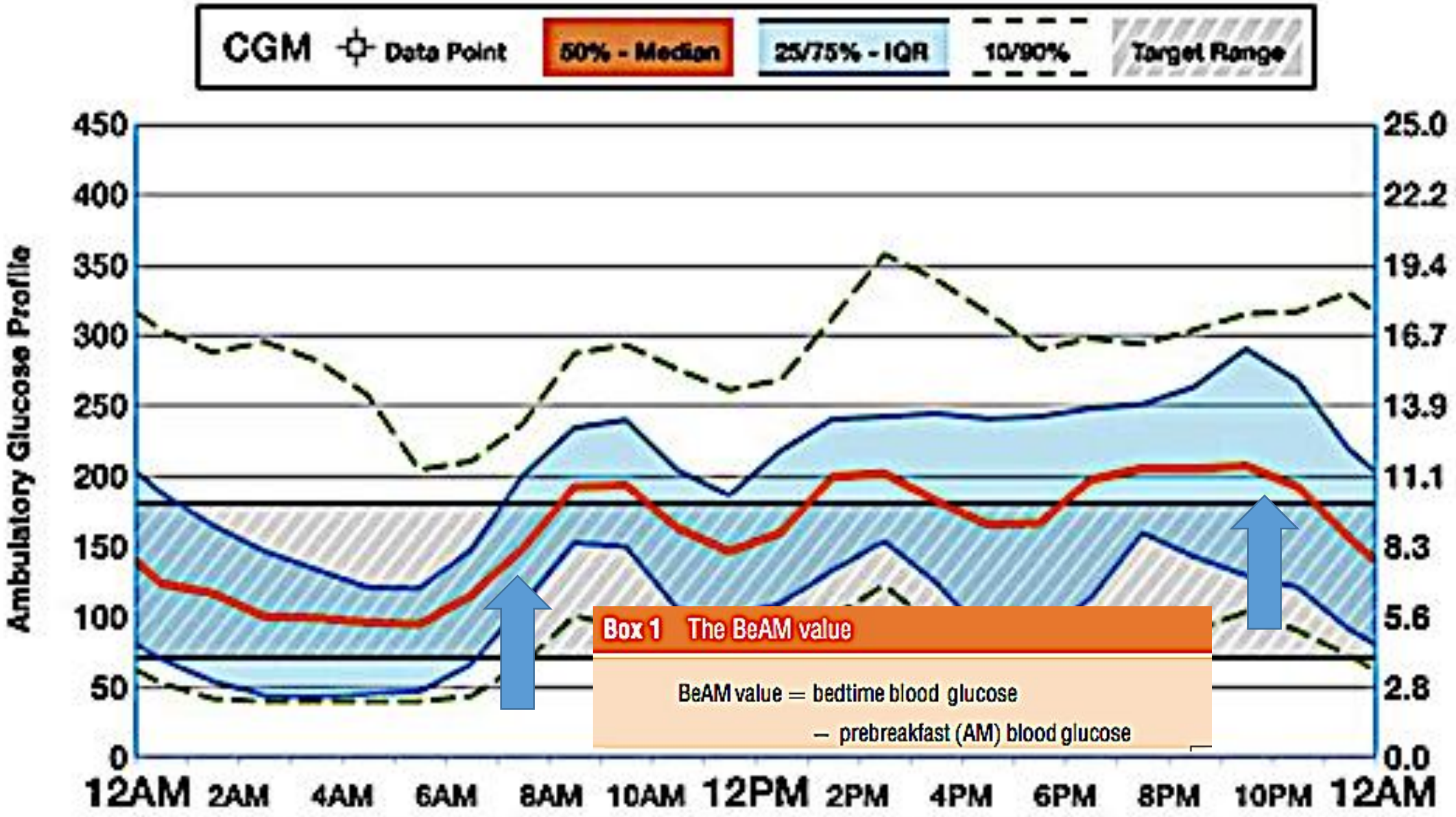
Box 1 The BeAM value

BeAM value = bedtime blood glucose
– prebreakfast (AM) blood glucose

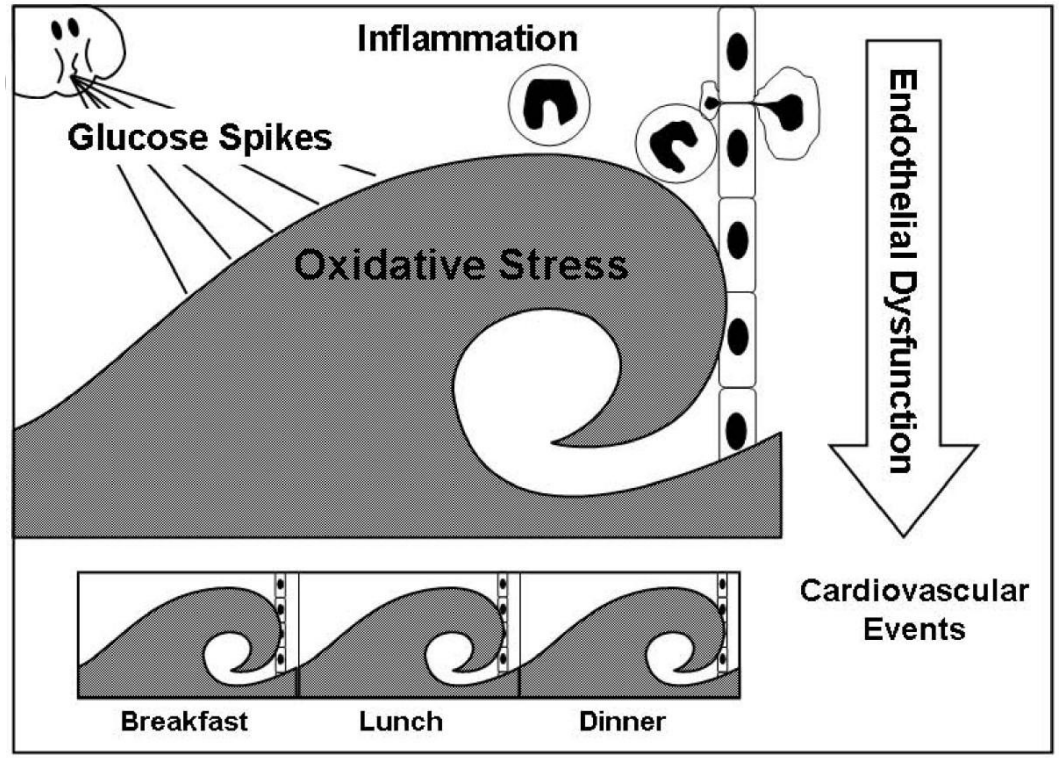


The BeAM is a simple, easy-to-calculate value that may identify patients with type 2 diabetes mellitus using basal insulin whose postprandial glucose needs targeting.

BMJ Open Diabetes Research and Care 2016;4:e000171


CGM
Data Point
50% - Median
25/75% - IQR
10/90%
Target Range
Ambulatory Glucose Profile
450
400
350
300
250
200
150
100
50
0
25.0
22.2
19.4
16.7
13.9
11.1
8.3
5.6
2.8
0.0
12AM
2AM
4AM
6AM
8AM
10AM
12PM
2PM
4PM
6PM
8PM
10PM
12AM
Box 1 The BeAM value
BeAM value = bedtime blood glucose
– prebreakfast (AM) blood glucose
The Y axis scale and target range are the same as on the Ambulatory Glucose Profile graph above.

Le complicanze della iperglicemia postprandial



IDF Guideline for Management of Postmeal Glucose in Diabetes 2011

- L'iperglicemia postprandiale si associa a
  - malattie cardiovascolari
  - retinopatia
  - tumori
  - disturbi cognitivi
  - aterosclerosi asintomatica
  - stress ossidativo, infiammazione e disfunzione endoteliale

Il controllo a due dimensioni

Pathophysiological impacts of the excessive glycation of proteins and the activation of oxidative stress on the risk of diabetic complications (diagonal solid arrow).

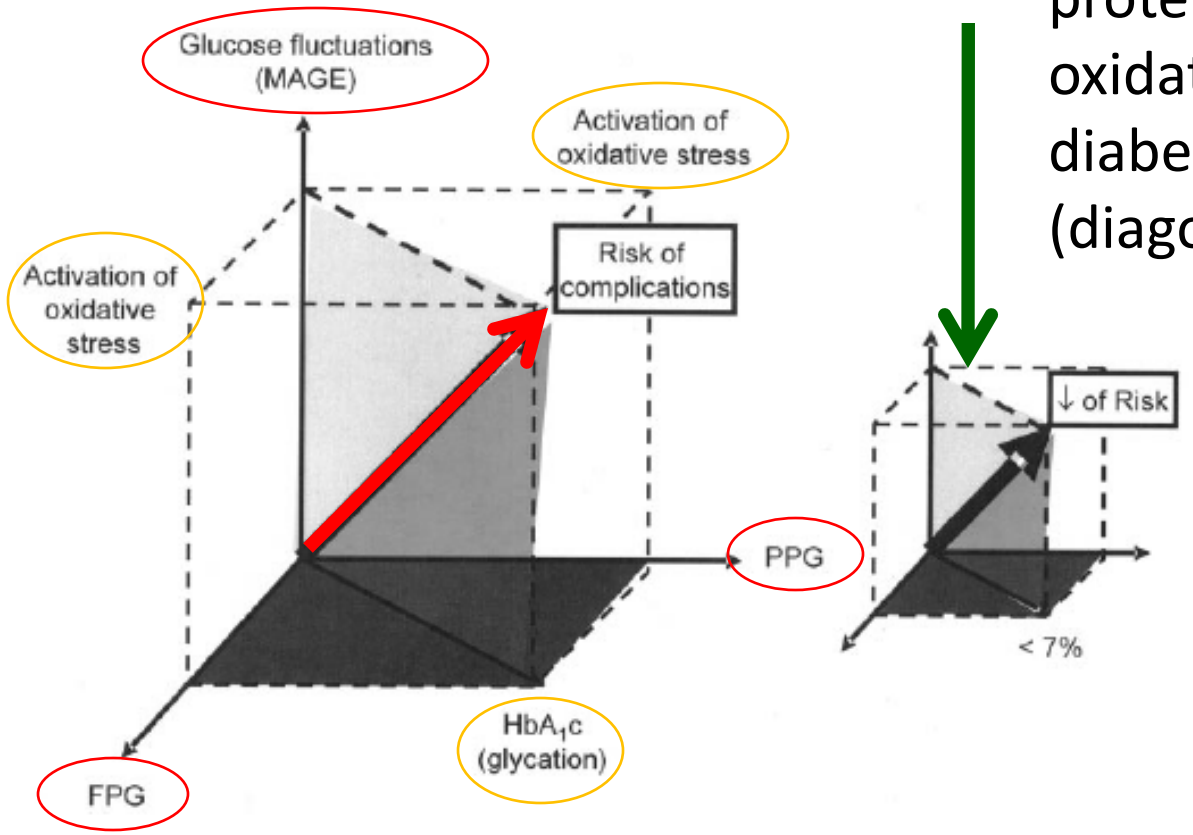


Figure 2—*Model suggested for illustrating the pathophysiological impacts of excessive glycation of proteins and activation of oxidative stress on the risk of diabetes complications (diagonal solid arrow). The contributions of the three components of dysglycemia, i.e., hyperglycemia at fasting (fasting plasma glucose [FPG]), hyperglycemia during postprandial periods (postprandial glucose [PPG]), and acute glucose fluctuations (MAGE), are indicated on the x, y, and z axes, respectively.*

Monnier L Diabetes Care 2008: 31 (Suppl. 2): S150– S154 2008

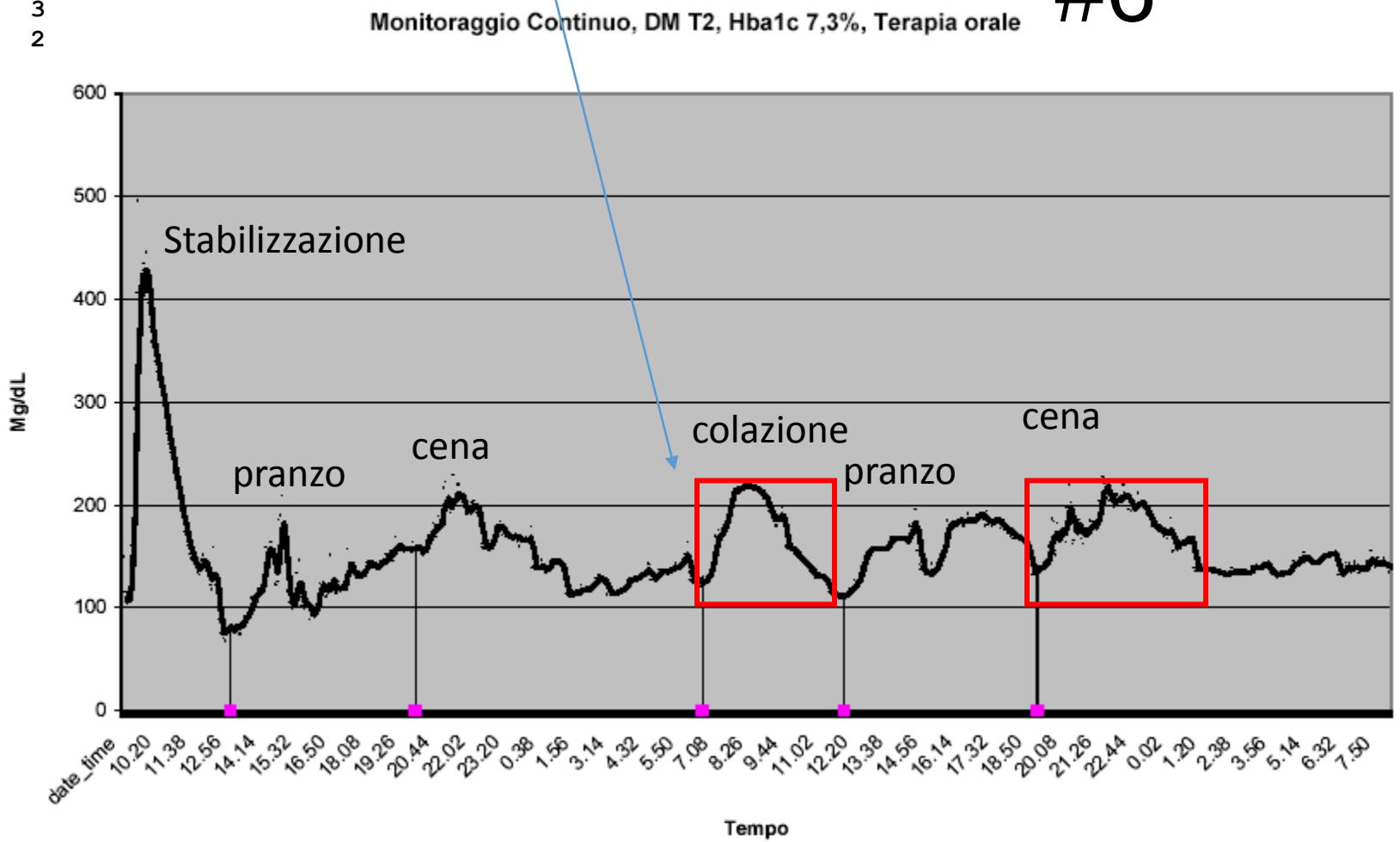
Immettere il valore per paz: 5662

Andamento Emoglobina glicata

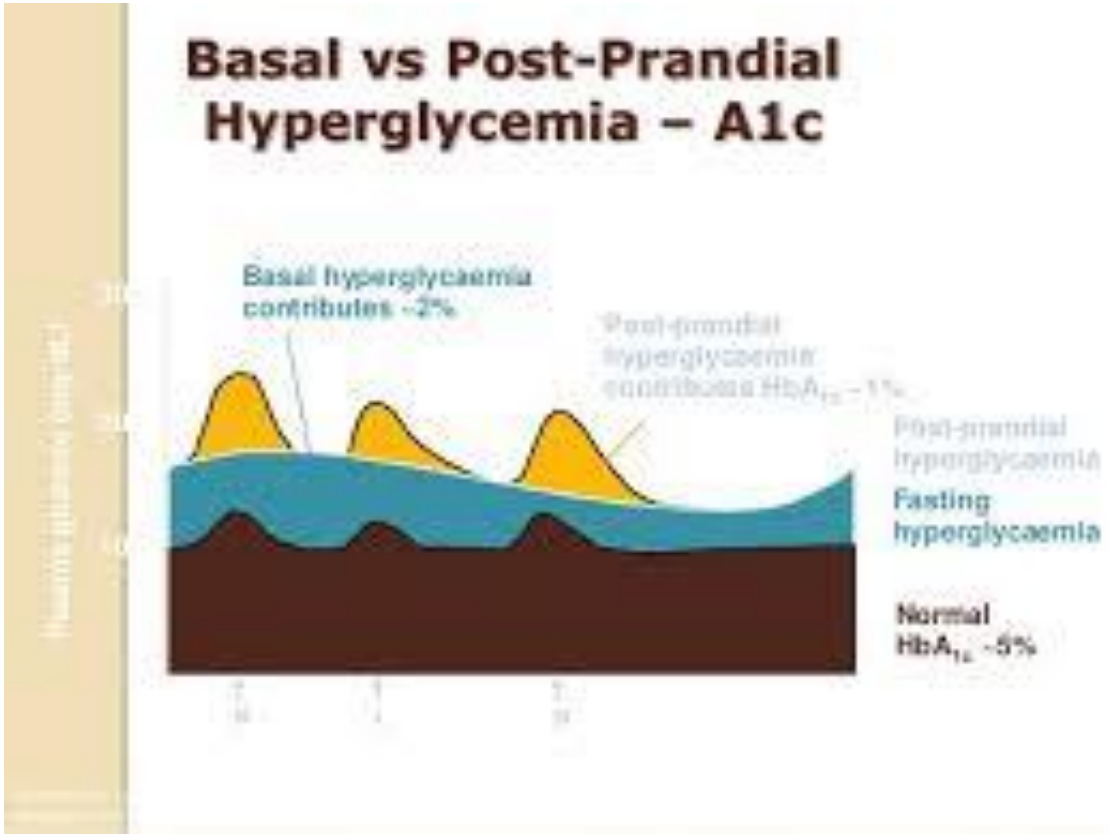
ES_COD_PAZ	ANNO	MEDIA	STDEV	MIN	MAX	ESAMI
5662	1995	6.40	.85	5.80	7.00	2
	1996	6.25	.35	6.00	6.50	2
	1997	6.10	.28	5.90	6.30	2
	1998	6.25	.07	6.20	6.30	2
	1999	7.35	.64	6.90	7.80	2
	2000	7.65	1.06	6.90	8.40	2
	2001	7.57	1.95	6.20	9.80	3
	2002	7.15	.21	7.00	7.30	2
**********		------		------	------	
avg		6.84				
minimum				5.80		
maximum					9.80	
std		.65				

Data		Mod.	Colaz.	Mat.	Pranzo	Pom.	Cena	notte
24/04/02	Me	AU	157		115	100		
12/04/02	Ve	AU	189		98	99		156
22/11/01	Gi	AU	158		112	116		

Caso #6

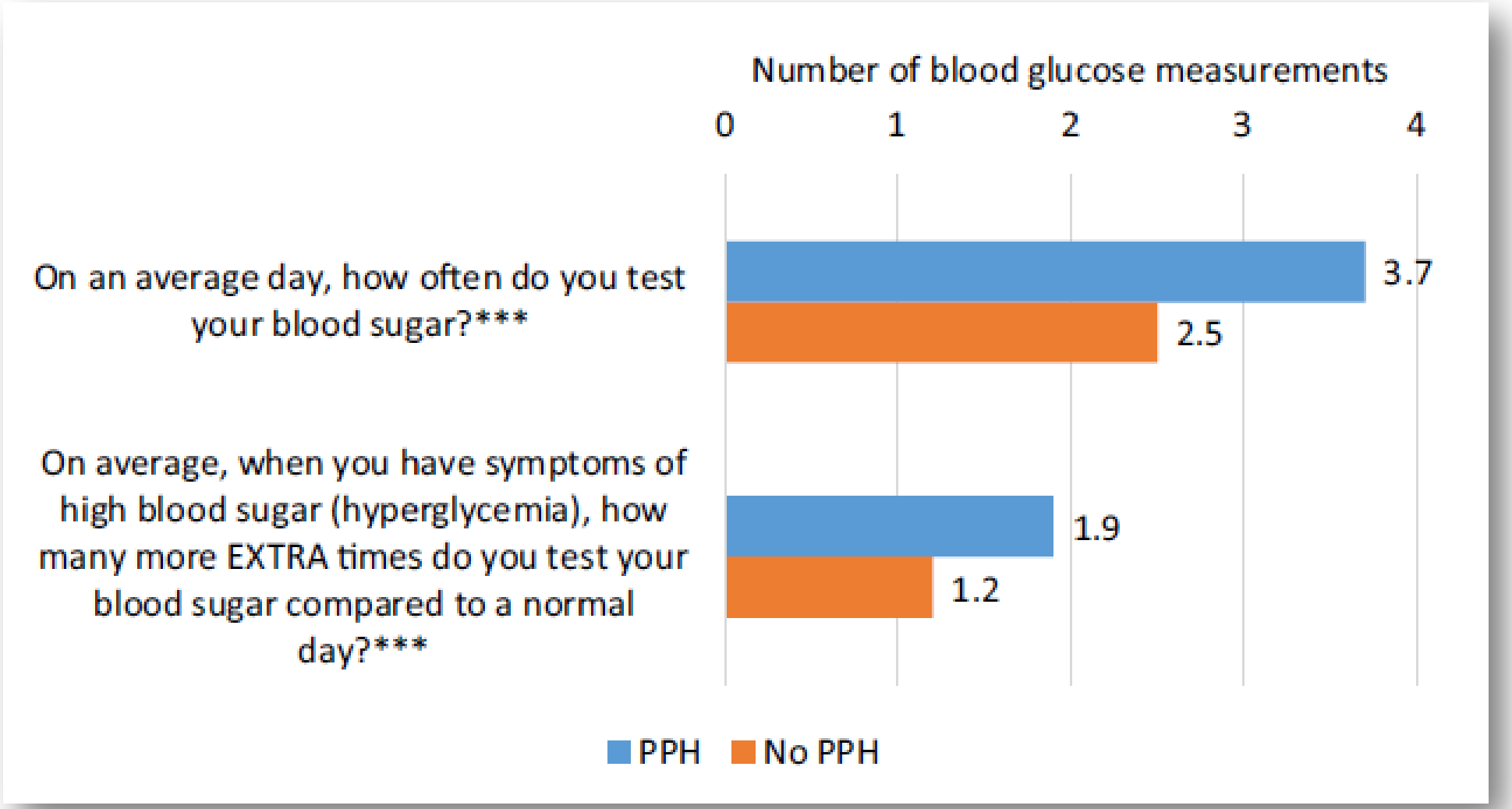


impatto economico della iperglicemia postprandiale



Curtesy Concetta Irace

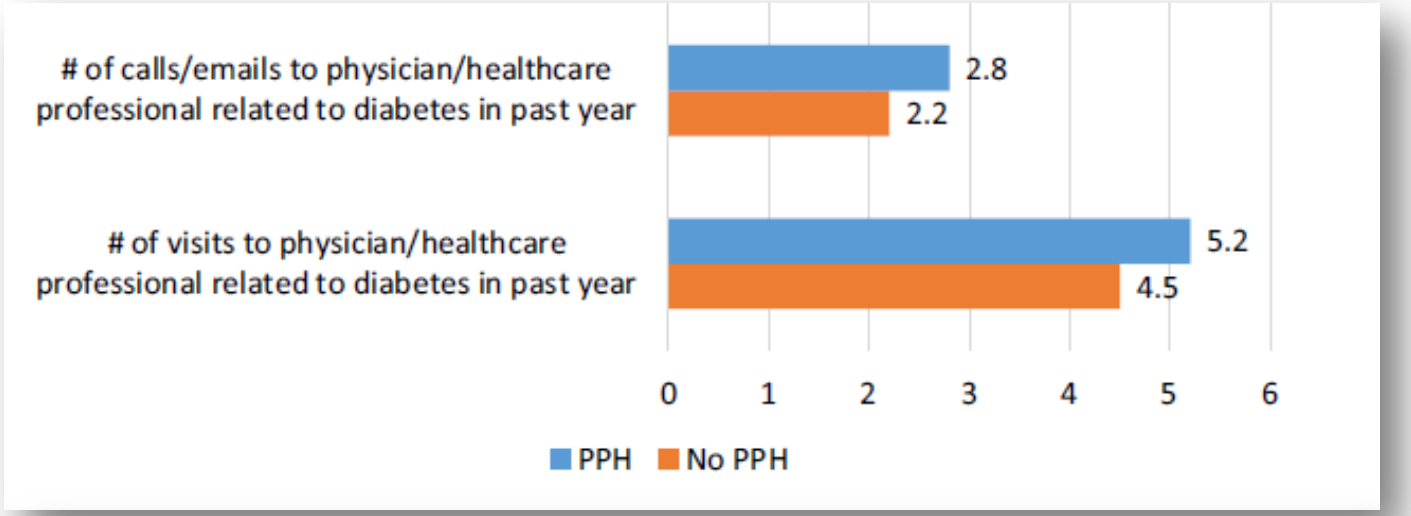
The Economic Burden of Post-Prandial Hyperglycemia (PPH)Among People with Type 1 and Type 2 Diabetes in Three Countries



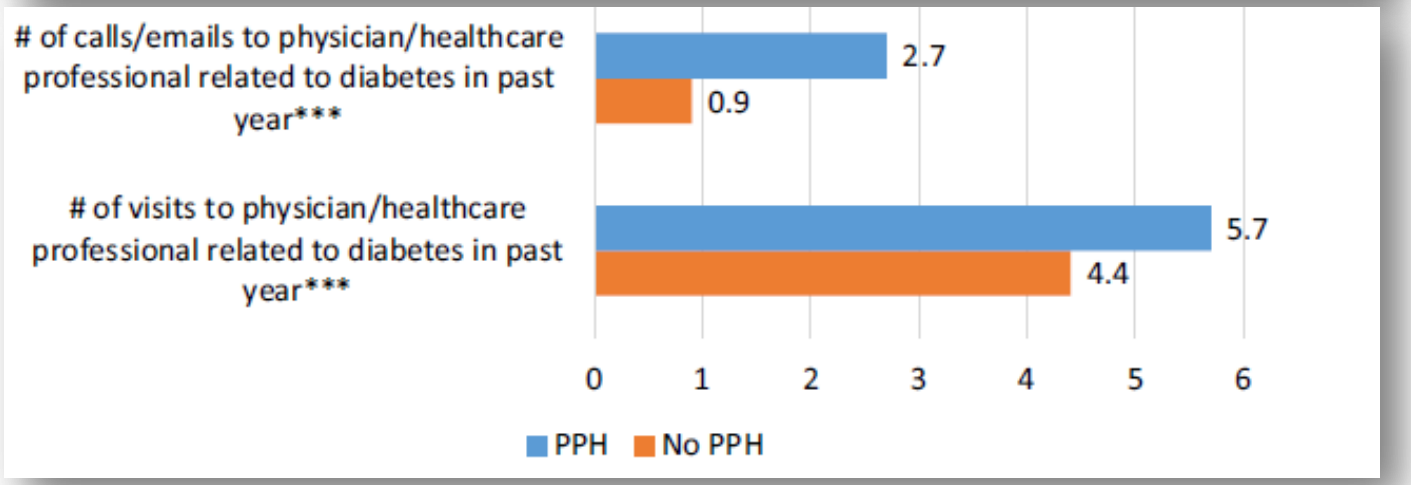
Curtesy Concetta Irace

Brod et al. Diabetes Ther 2016

The Economic Burden of Post-Prandial Hyperglycemia (PPH)Among People with Type 1 and Type 2 Diabetes in Three Countries



Type 1



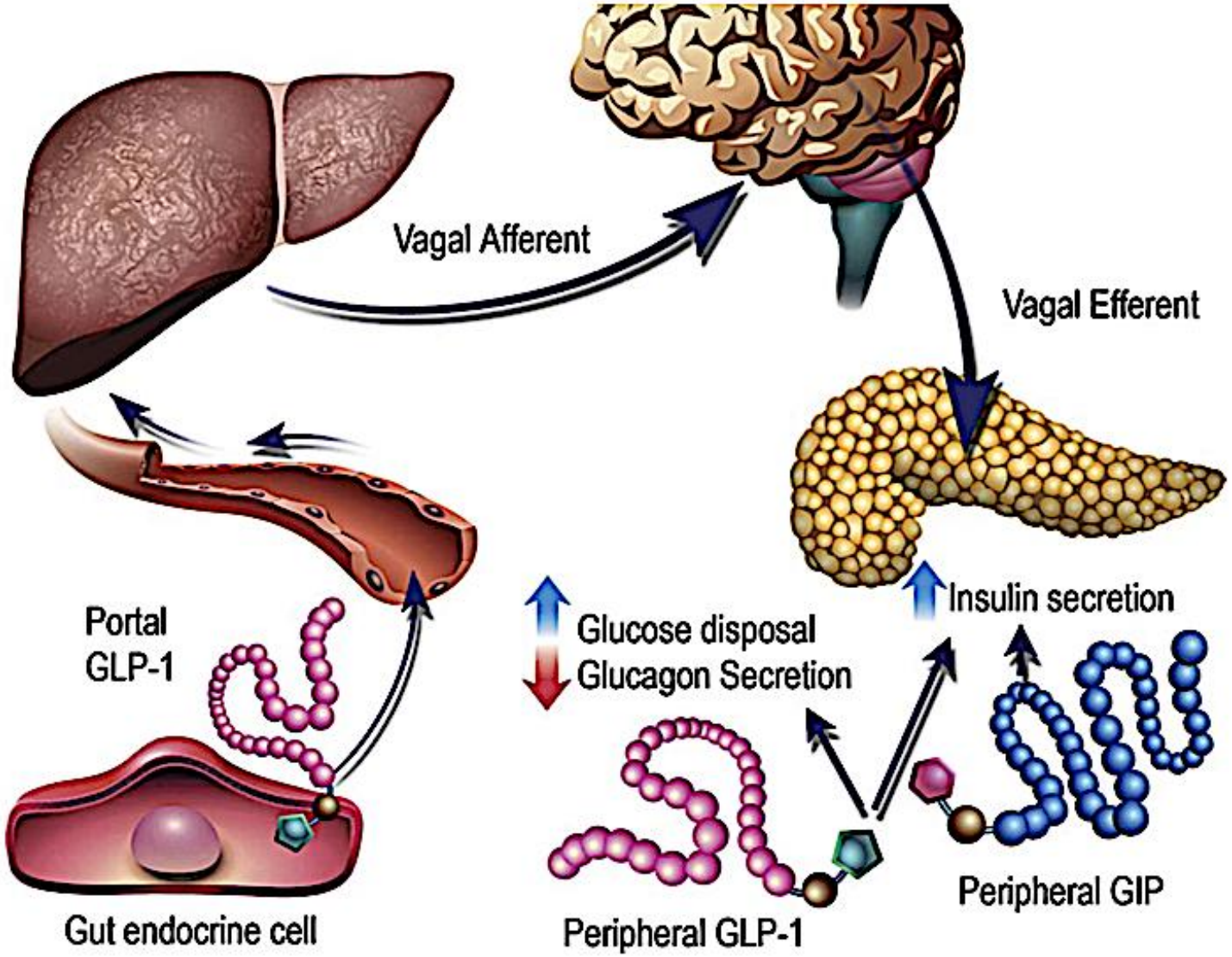
Type 2

Curtesy Concetta Irace

Brod et al. Diabetes Ther 2016

La terapia della iperglicemia postprandiale: Ruolo dell'insulina prandiale…..

GLP-1 and Insulin secretion



CELL METABOLISM 3, 153–165, MARCH 2006

Therefore, the problem has to be that the β-cell response to GLP-1 following meal ingestion is deficient, as shown following intravenous administration of GLP-1 under controlled conditions (Diabetes Care. 2003; 26:791–798).

This deficient response is in keeping with a more global deficiency in β-cell responsiveness to numerous secretagogues including sulphonylureas, amino acids, and β- adrenoreceptor agonists (Diabetes Care. 1984; 7:491–502).

Linee Guida

Il diabete tipo 2 è caratterizzato da un progressivo declino della massa e della funzione beta cellulare. Pertanto in una fase più o meno precoce della storia naturale del diabete tipo 2 la terapia insulinica è necessaria

- *iniziare preferibilmente con una basale*
- *utilizzare direttamente uno schema basal-bolus*
- *utilizzare un analogo rapido ai pasti*

AMD-SID 2014

I soggetti con glicemie non controllate o con iperglicemie sintomatiche e già in trattamento con insulina basale posso beneficiare di un trattamento combinato basale+bolo. L'approccio più semplice è quello di *aggiungere una singola iniezione di analogo rapido al pasto principale* (5 UI o 10% della basale). Il regime basal bolus è più efficace e flessibile (50% della TDD in 3 boli). Le modifiche non devono superare il 10-20% o 1-2 UI ogni 2-3 giorni. La titolazione si effettua considerando le glicemie postprandiali o le glicemie che precedono il pasto successivo.

AACE/ACE 2016

6.5. New drugs for patients with type diabetes

6.5.1. Burden of type 2 diabetes

Given that diabetes is a more heterogenic disease than previously thought, the more recent recommendations advocate personalizing diabetes care

Choosing wisely among the treatment options available is difficult, given the limited number of comparative effectiveness and safety studies conducted in the area. The effectiveness and safety of new drugs should be demonstrated in studies versus current optimal treatment.

Analoghi rapidi disponibili

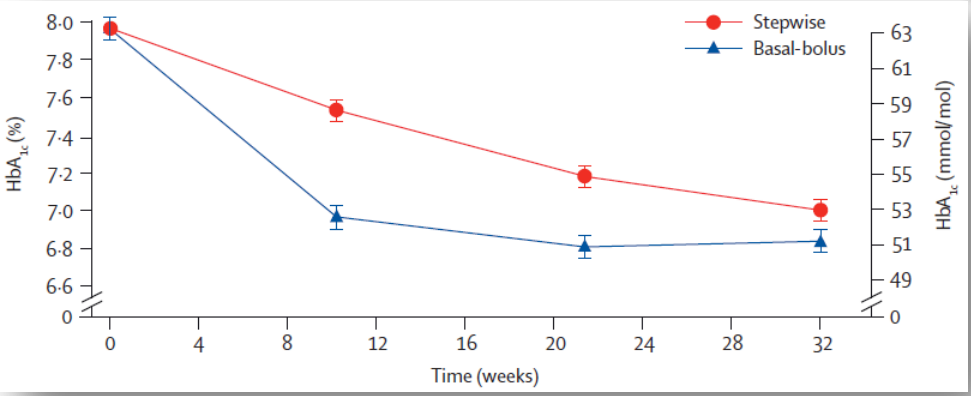
Product	Adults	Infusion SC+IV	Children (6 y-o)	Kidney failure	Children (>2 y-o)	Liver Impairment	Pregnant women	Elderly
Aspart[1]	X	X	X	X	X (>2 y)	X	X SPC: Prospective data (RCT)	X Indication validated by a PK/PD study
Lispro[2]	X	X	X	X	X	X	X Retrospective data	X No dedicated study
Glulisine[3]	X	X Incom-patibility with Glucose and Ringer's solution	X	X	No authori zation	No study	No data	X No dedicated study

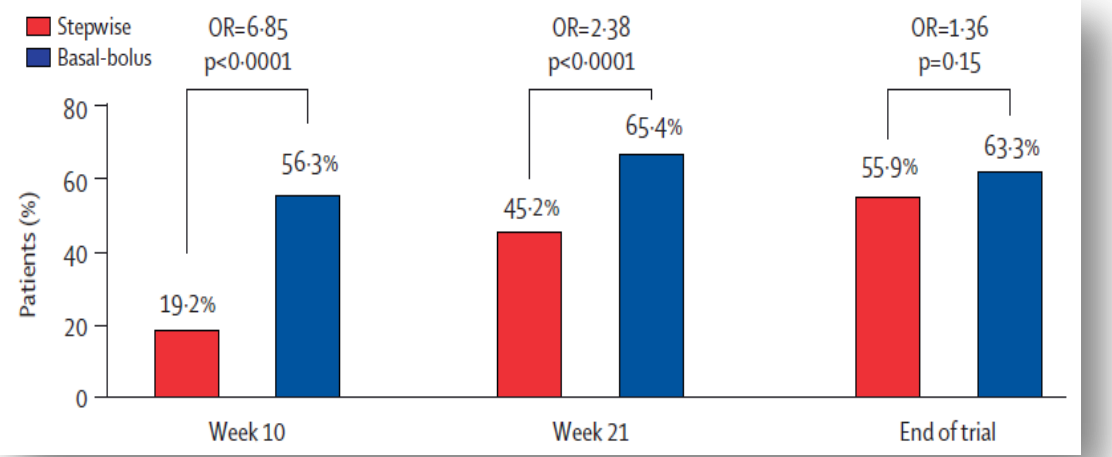
	Duration of vial conservation	Maximal T° for vial conservation (after opening)
Aspart[1]	**30 MONTHS**	**4 WEEKS AT 30° C**
Lispro[2]	**24 MONTHS**	**4 WEEKS AT 30° C**
Glulisine[3]	**24 MONTHS**	**4 WEEKS AT 25° C**

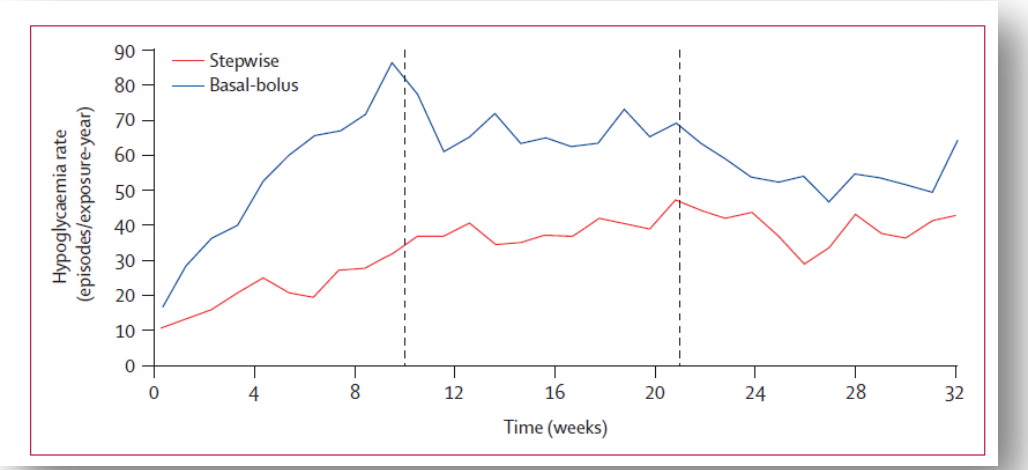
Differenti schemi di intensificazione insulinica

Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial

Helena W Rodbard, Virginia E Visco, Henning Andersen, Line C Hiort, David H W Shu

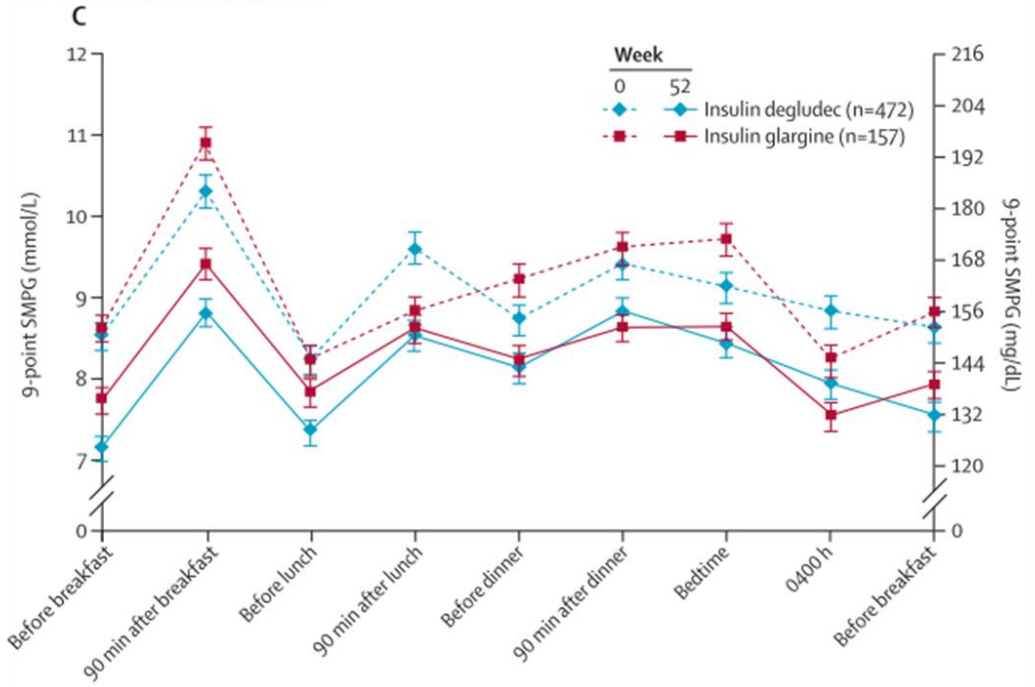






Intensificazione in associazione con nuove insuline basali

BEGIN Basal-Bolus Type 1 - Glycaemic efficacy in the insulin degludec and insulin glargine groups

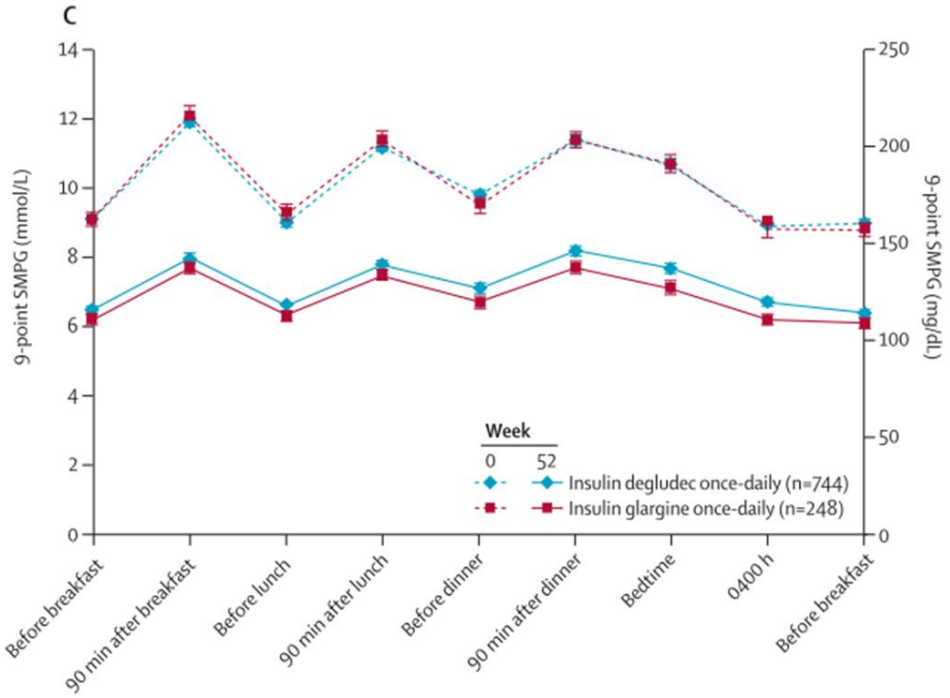


Heller S et al. Lancet 2012

IDeg vs IGlarg

- Total basal insulin -14%
- Total bolus insulin -10%
- TDI -11%

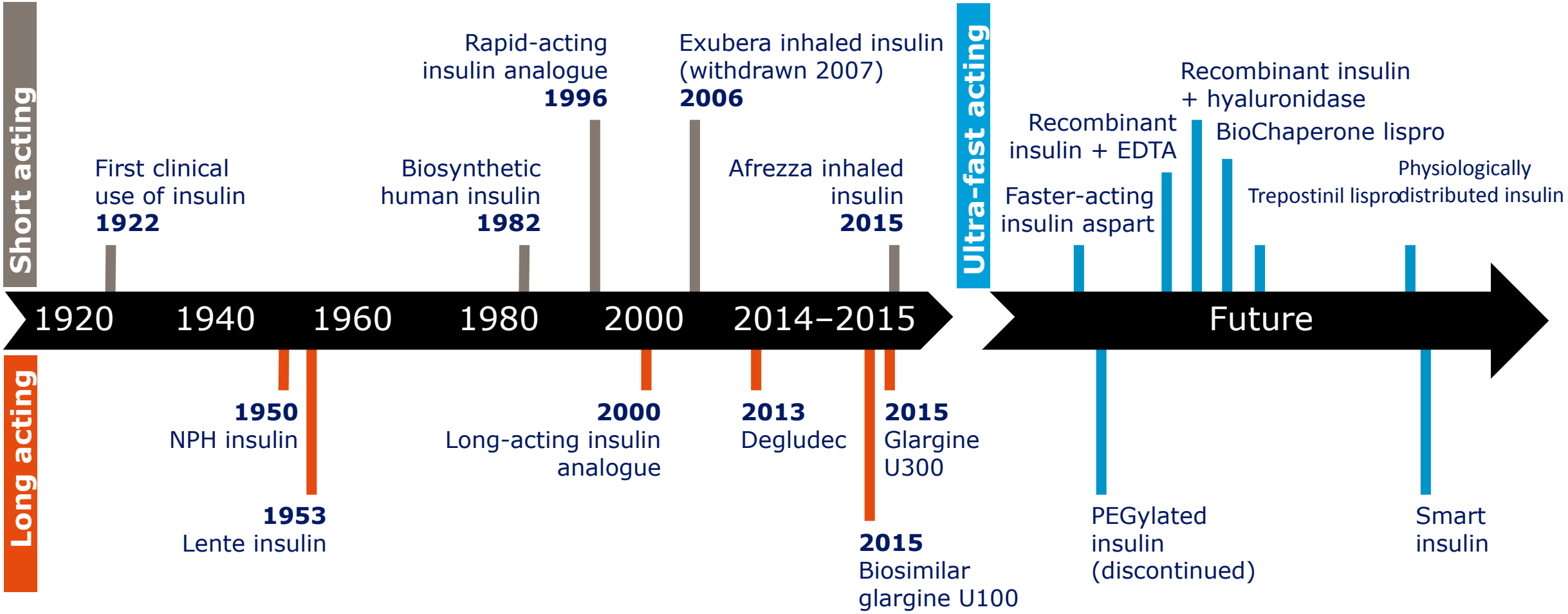
BEGIN Basal-Bolus Type 2: 9-point profiles from self-measured plasma glucose at baseline (week 0) and after 52 weeks



Garber AJ et al. Lancet 2012

Futuro Prossimo

Goal of insulin development: approach endogenous insulin secretion by healthy pancreatic beta cells

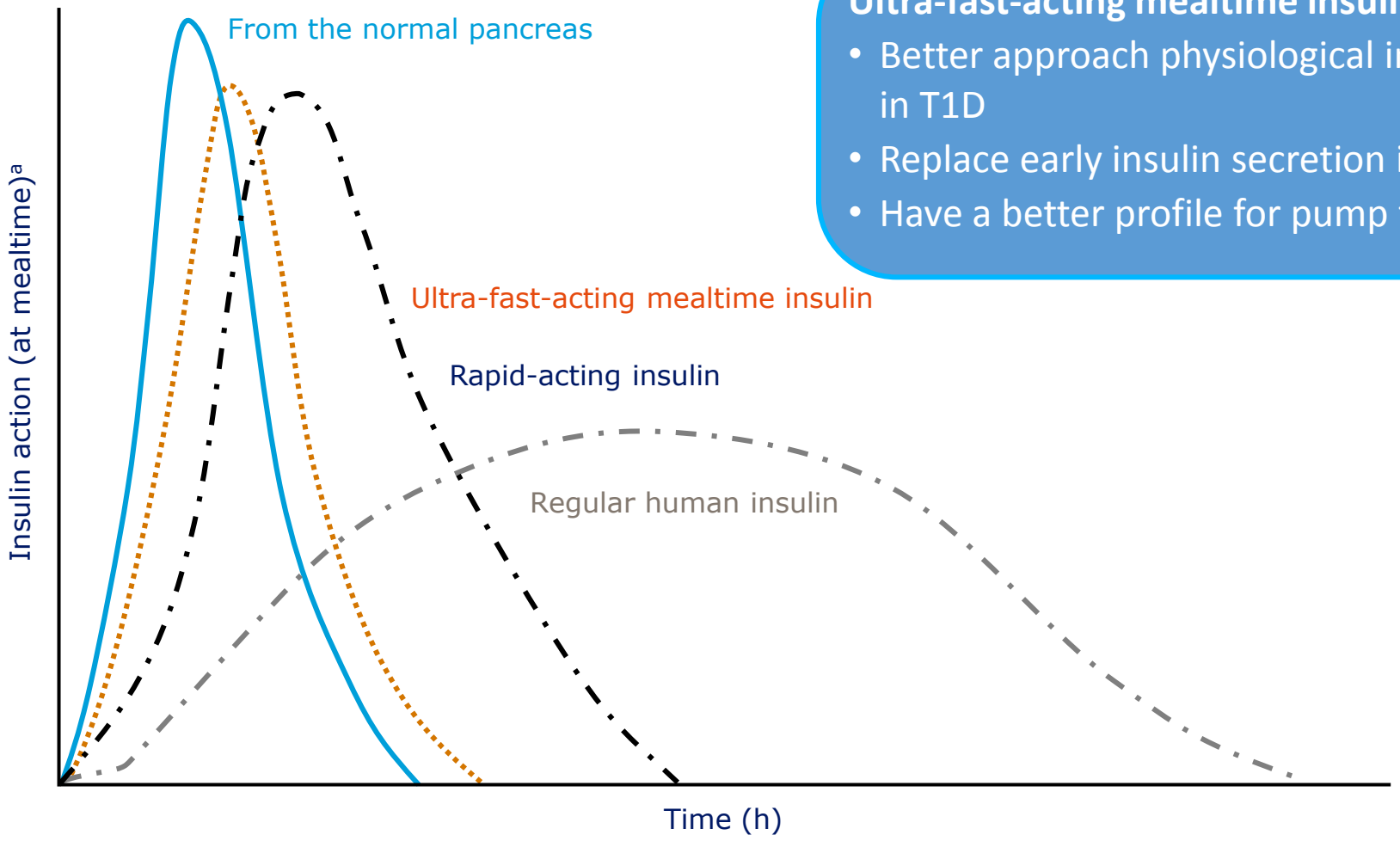


Adapted from Cahn A et al. *Lancet Diabetes Endocrinol* 2015;3:638–652.
Eli Lilly Patent Application 12 Nov 2015; Eli Lilly Press Release 4 Dec 2015; Novo Nordisk Capital Markets Day R&D update 19 Nov 2015

Ultra-fast-acting mealtime insulins: approaching physiological insulin profile even further

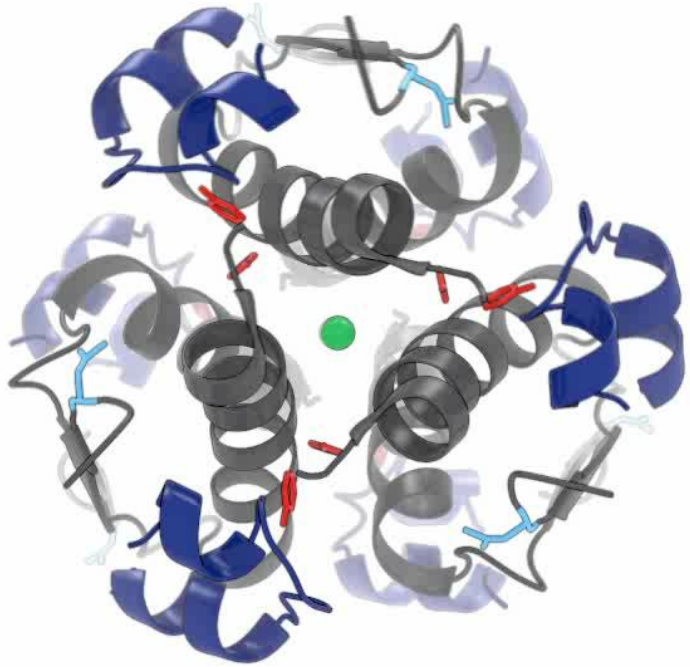
Ultra-fast-acting mealtime insulin should:

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Have a better profile for pump therapy



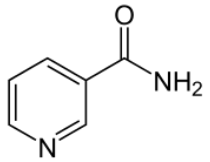
[a]Schematic representations. T1D, type 1 diabetes; T2D, type 2 diabetes.Adapted from Home PD. Diabetes Obes Metab 2015;17:1011–20.

Changing the formulation: Faster aspart is insulin aspart in a new formulation



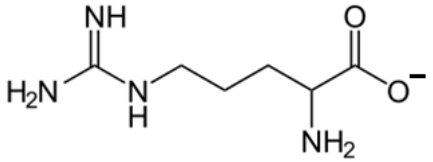
Insulin aspart

Niacinamide: absorption modifier



Vitamin B3

L-Arginine: added for stability



Naturally occurring amino acid

FDA's Inactive Ingredient Search for Approved Drug Products database. Available from: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last accessed April 2015

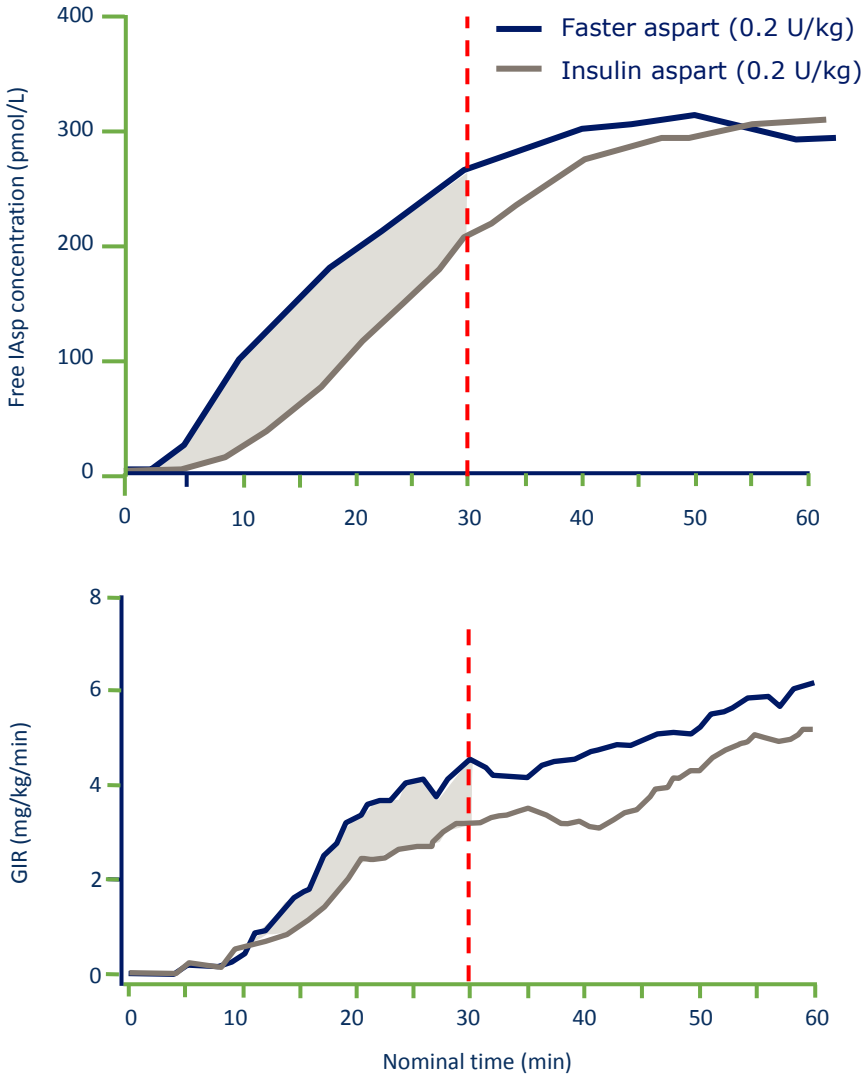
What do we know about faster aspart via s.c. injection?

Compared with insulin aspart, faster aspart has:

Twice as fast onset of appearance in the bloodstream

Twofold higher insulin exposure within the first 30 min

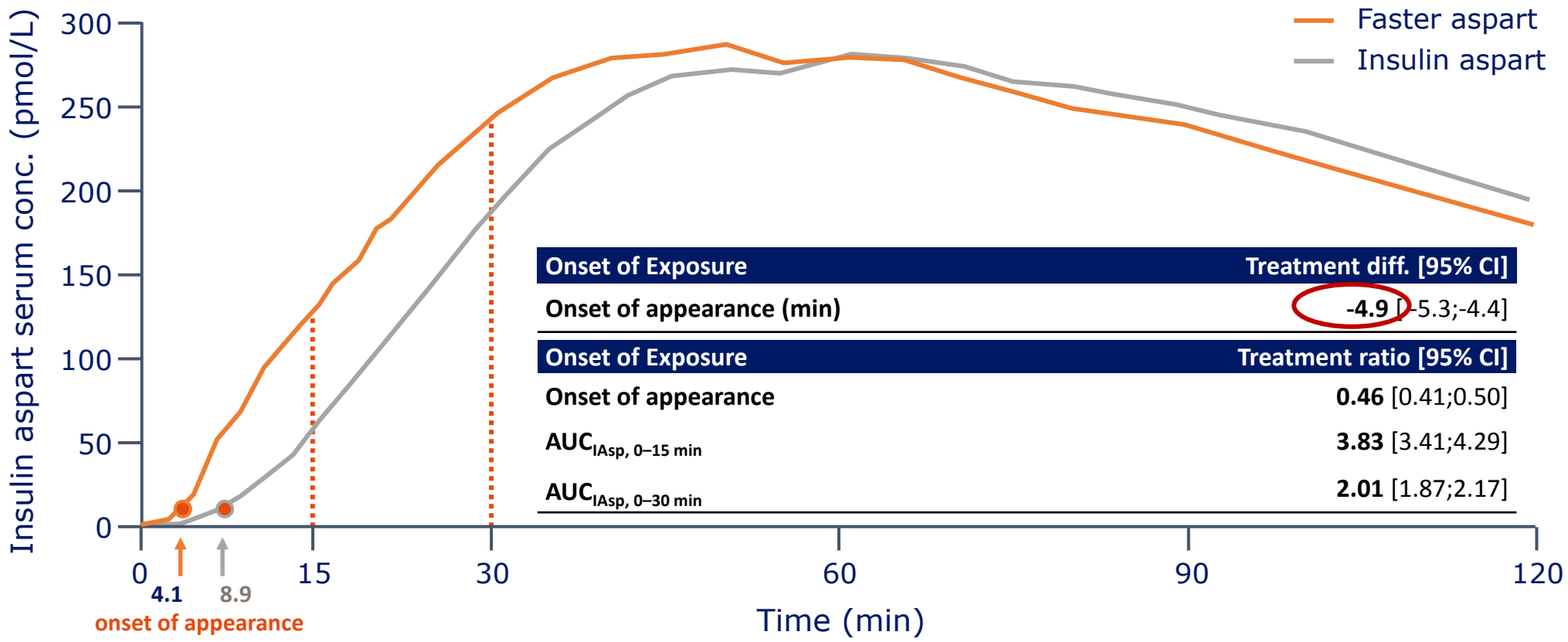
>50% greater insulin action within the first 30 min



Faster aspart, faster-acting insulin aspart; GIR, glucose infusion rate; IAsp, insulin aspart; s.c., subcutaneous. Heise T et al. Diabet Obes Metab 2015; 17:682–8; Shiramoto M et al. Diabetes 2015; Suppl 1:A249; Hövelmann U et al. Diabetologia 2015; Suppl 1:933P.

PK – Onset of exposure

Pooled analysis 6 studies



Onset of Exposure	Treatment diff. [95% CI]
Onset of appearance (min)	**-4.9** [-5.3;-4.4]

Onset of Exposure	Treatment ratio [95% CI]
Onset of appearance	**0.46** [0.41;0.50]
$AUC_{IAsp,\ 0–15\ min}$	**3.83** [3.41;4.29]
$AUC_{IAsp,\ 0–30\ min}$	**2.01** [1.87;2.17]

Twice as fast onset of appearance in the bloodstream

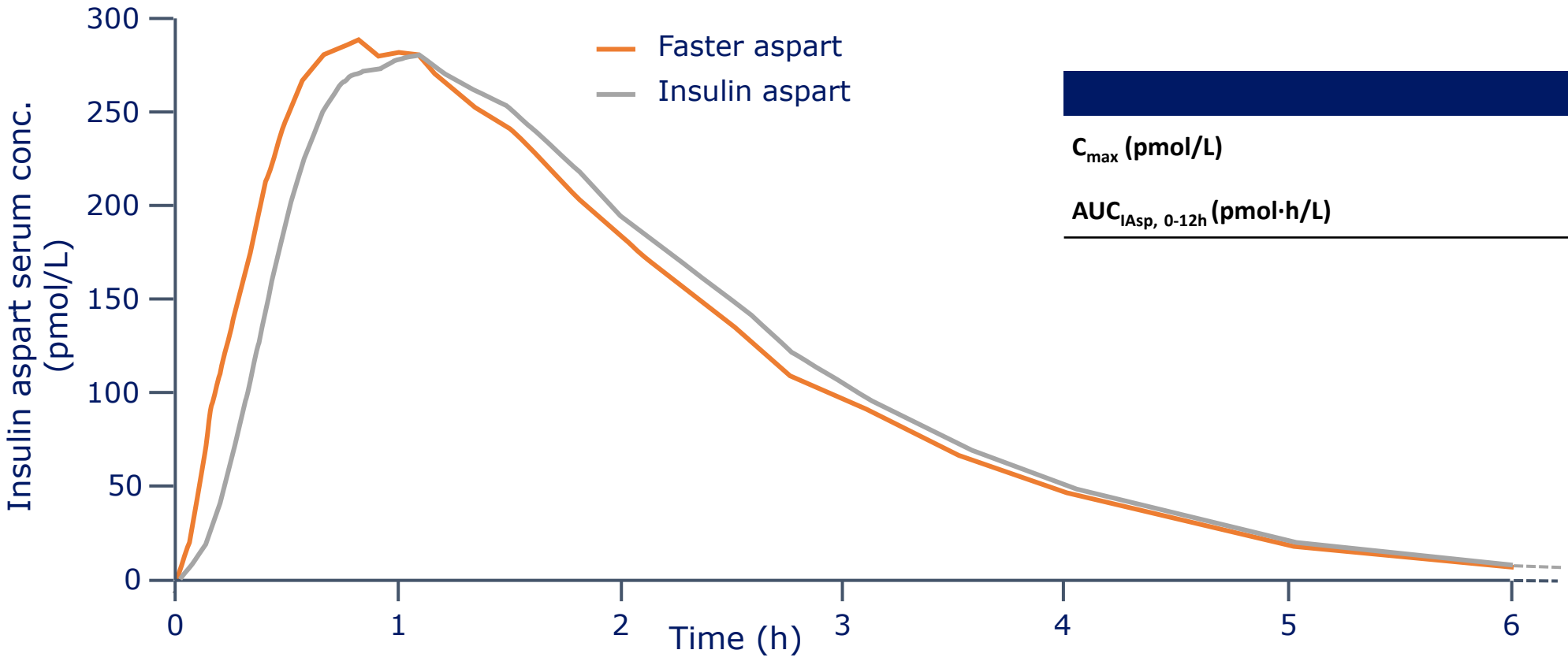
Two-fold higher insulin exposure within the first 30 minutes

AUC, area under the curve; CI, confidence interval

Heise T et al. *Diabetes* 2016;65(S1):A239.

PK – Total and Maximum exposure

Pooled analysis 6 studies



	Ratio [95%CI]
C_{max} (pmol/L)	**1.04** [1.00;1.08]
$AUC_{IAsp,\ 0\text{-}12h}$ (pmol·h/L)	**1.01** [0.98;1.04]

Similar total and maximum exposure

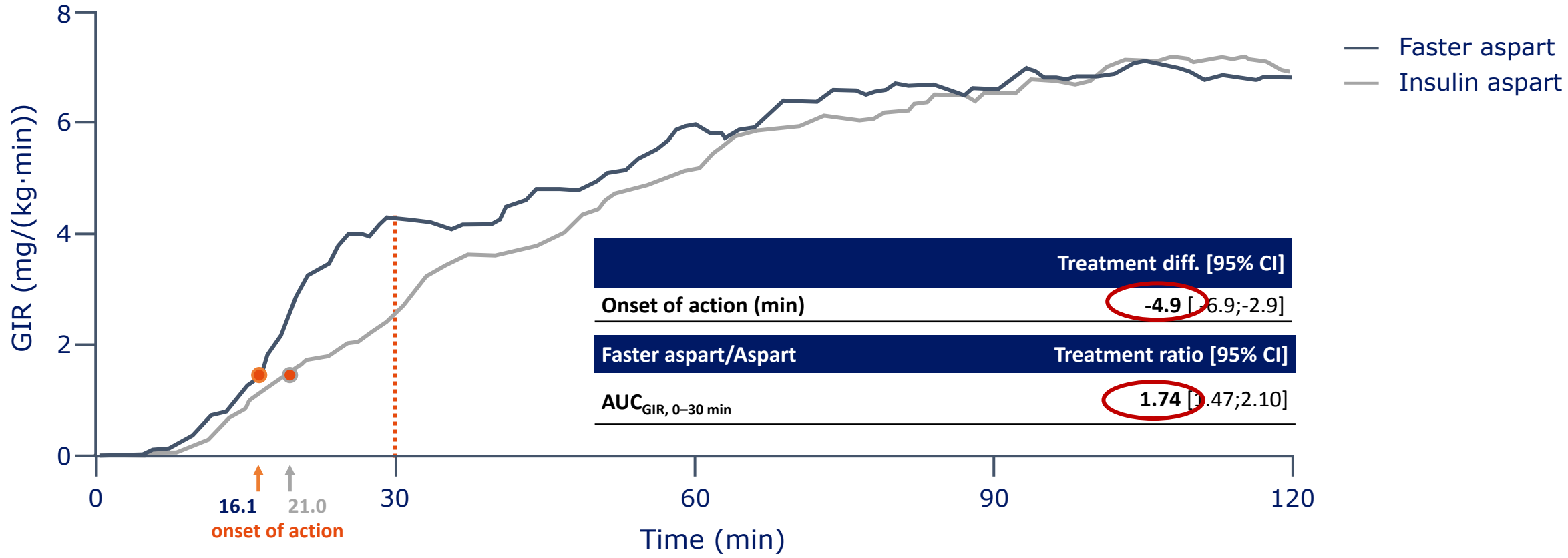
C_{max} ratio p=0.085

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; IAsp, insulin aspart

Heise T et al. *Diabetes* 2016;65(S1):A239.

PD – Early glucose-lowering effect

Pooled analysis 3 studies



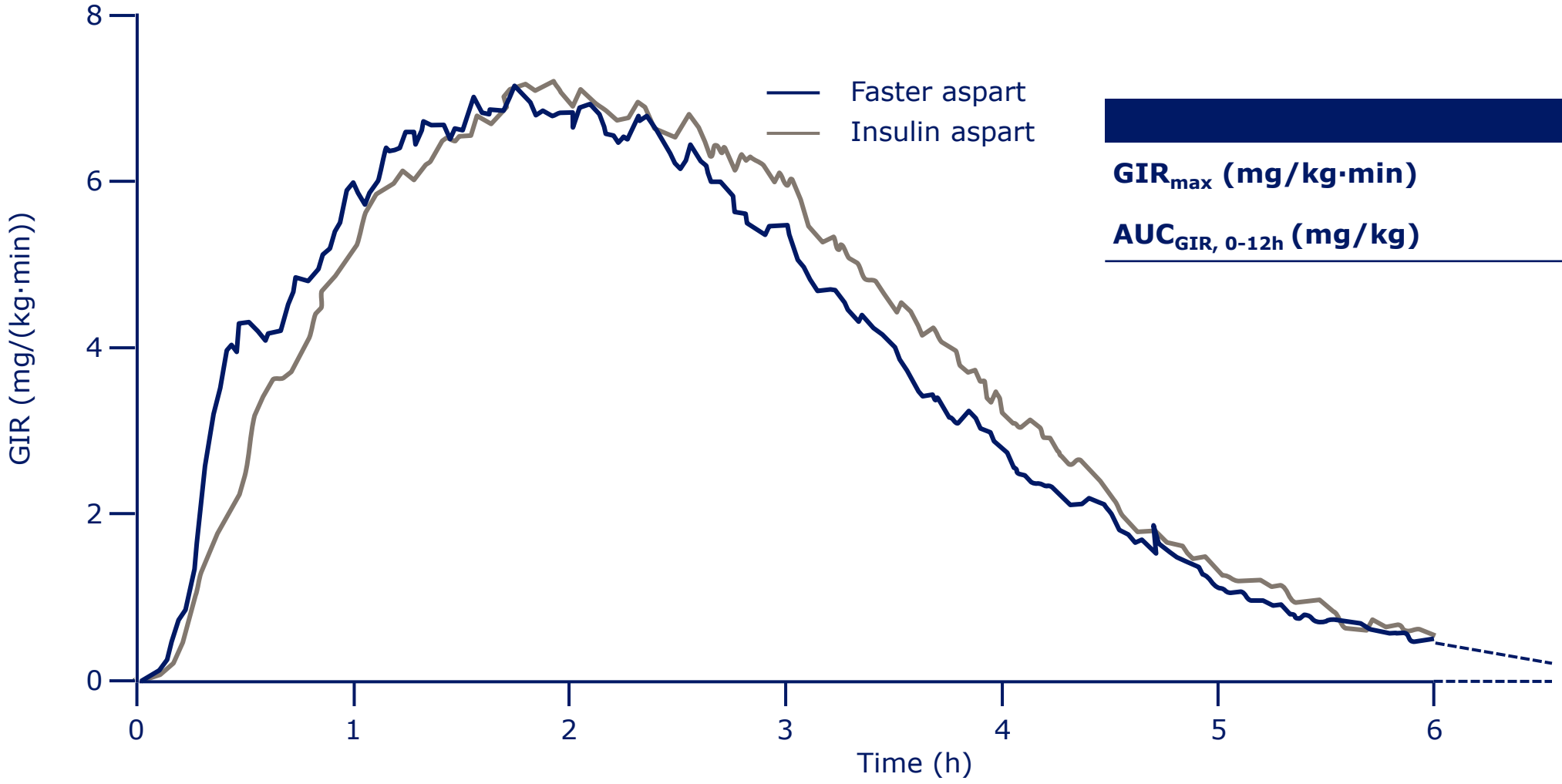
>50% greater insulin action within the first 30 minutes

AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate

Heise T et al. *Diabetes* 2016;65(S1):A239.

PD – Total and Maximum glucose-lowering effect

Pooled analysis 3 studies



	Ratio [95%CI]
GIR_{max} (mg/kg·min)	**1.01** [0.96;1.05]
$AUC_{GIR,\ 0\text{-}12h}$ (mg/kg)	**0.98** [0.94;1.03]

AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate

Heise T et al. *Diabetes* 2016;65(S1):A239.

- Despite an increased awareness of a strong association between postprandial or postchallenge hyperglycemia and cardiovascular risk and in spite of direct recommendations from their providers, many patients do not routinely monitor PPG, and it is perceived as being inconvenient and disruptive of their daily routine.

- Sorkin JD, Muller DC, Fleg JL, et al. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. Diabetes Care 2005;28:2626–32.
- Levitan EB, Song Y, Ford ES, et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004;164:2147–55.
- Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006;91:813–19.
- Choi JH, Park CY, Cha BS, et al. Perception of clinicians and diabetic patients on the importance of postprandial glucose control and diabetes education status: a cross sectional survey. Diabetes Metab J 2012;36:120–7.
- Ong WM, Chua SS, Ng CJ. Barriers and facilitators to self-monitoring of blood glucose in people with type 2 diabetes using insulin: a qualitative study. Patient Prefer Adherence 2014;8:237–46.

Considerazioni conclusive

- Diabete tipo 1 e 2 si accompagnano ad iperglicemia post-prandiale
- L'iperglicemia post-prandiale è determinata dall'introito di carboidrati e dal deficit di secrezione insulinico
- Si associa alle complicanze croniche del diabete ed è responsabile dello stress ossidativo
- La terapia con insulina ad azione …..rapida….. e insulina basale rappresenta un modello efficace di controllo della glicemia
- E' necessario avvicinarsi sempre di più al profilo insulinico fisiologico con un'insulina ai pasti più rapida